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BERKELEY 4, CALIFORNIA

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Dr. Rosalind Franklin
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21 Torrington Square, W.C. 1
London, England

Dear Rosalind:

I found your enclosed MS very interesting to read. First I will comment about the MS and then I will try to answer the questions in your letter. I have shown your paper to Dr. Fraenkel-Conrat, and so my comments include his.

1. I find that there is a great diversity in the apparent thickness of the "doughnuts" obtained by lowering the pH of an A-protein solution. It is at least as great as the variation quoted (50-150 A), and from the electron microscopic evidence, I would say the material is far from monodisperse. It has not been examined critically here in the ultracentrifuge, but the preliminary evidence shows the boundary to be quite broad. From inspection of the micrographs published by Schramm (with thin, "soft" shadows) I do not see how he can obtain anything but the roughest notion of the "doughnut" thickness.

2. I agree with your conclusion that the most energetically favorable way to go from A-protein to "doughnuts" is by the side-to-side aggregation you propose. It also seems likely that the completion of one helical portion (a "doughnut") would represent a distinct "full-stop" in the aggregation process. I am a little worried by the mechanics of the fitting of the last A-protein unit into the helix; it would have to be aligned exactly, and during the alignment there would be no side-to-side forces upon it.

3. I would advise you not to draw any significant conclusions from the micrographs of Schramm and Zillig as shown in the recent Z. f. Naturforsch. These are the only micrographs I have seen, of course, alleging to show a striated appearance, and you may have seen better ones. These micrographs are truly dreadful; they are severely underfocussed and show marked evidence of either astigmatism or of image drift. From micrographs of this character one cannot conclude anything about the reality of striated appearances. Native TMV itself will show beautiful cross-markings when photographed so poorly, as my poorer micrographs will demonstrate. I am going to obtain some first-class micrographs of aggregated A-protein, freshly made up, and will send you some prints. It may be that there is periodic structure on the rods, but it can be believed only if the quality of the micrographs is high. I think you weaken your paper by referring at this time to this dubious evidence.

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4. In connection with your last paragraph (p.7) we now find that the polymerization of the nucleoprotein apparently does not require the presence of "doughnuts" to start with. On the contrary, material which shows no sign of these, and which is presumably mostly A-protein, polymerizes very nicely. This is a relief, since the postulation of the threading of preformed discs upon the nucleic acid seems to make life a bit difficult. I would imagine that in this case the whole rod forms by a continuous wrapping of the A-protein elements around the nucleic acid, with some initial difficulty encountered after every 36 x-ray sub-units.

Now for the questions in your letter: The short fragments obtained by sonication of native TMV do at times give the appearance of having a depressed central region. Most of them do not, however. Even where this appearance is present, it is not clear that it corresponds to a "hole", as is so very clear in the case of the "doughnuts". To put it another way: I would conclude that the "doughnuts" certainly contain central holes; some of the sonicated fragments exhibit appearance of a central depression which might be interpreted as a hole.

I wish the word "doughnut" did not have to be used. Such objects are not in the gastronomic repertoire of all persons of all countries, and so strike some readers as foreign curiosities. Further, the word (or its misuse) has been pre-empted by the phage people to describe incomplete forms of the virus [see Levinthal and Fisher, Biochim. Biophys. Acta, 9, 419 (1952)]. Could they not be called "tori" or "perforated discs"? The former, a torus, is exactly the shape of a doughnut. I realize that both expressions are stodgy compared to the vivid "doughnut".

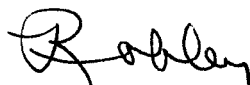
Whether or not the tori are of sufficiently uniform size to conclude that they are stopping points in the formation of a rod from the A-protein is a moot question. From my observations I would conclude that they are not; that they form a continuum from 50 A in thickness, and that above this thickness they are probably seen lying on their sides as very short rods.

I know of no study which has been made of the A-protein monomer by light-scattering. Someone ought to do it.

I will send you some micrographs soon, and will also include one showing the range of thickness exhibited by the tori.

With best regards,

Sincerely,



Robley C. Williams